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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/046,504	10/19/2001	Steven J. Siegel	P-9565-US	3358

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EXAMINER	
FUBARA, BLESSING M	

ART UNIT	PAPER NUMBER
1618	

MAIL DATE	DELIVERY MODE
09/03/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/046,504	SIEGEL ET AL.	
	Examiner	Art Unit	
	BLESSING M. FUBARA	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 June 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4 and 6-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4 and 6-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Examiner acknowledges receipt request for extension of time, amendment and remarks filed 6/02/08. Claims 4 and 10 are amended. Claims 1, 3, 4 and 6-10 are pending.

Response to Arguments

Previous rejections that are not reiterated herein have been withdrawn.

Claim Rejections - 35 USC § 103

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

2. Claims 1 and 3 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Cheng et al., "A poly(D,L-lactide-co-glycolide) microsphere depot system for delivery of haloperidol," in Journal of Controlled Release 55 (1998) 203-212 for reasons of record and reiterated herein below.

3. Cheng describes haloperidol-loaded biodegradable poly(D,L-lactide-co-glycolide) (PLG) microsphere (abstract), a 10% haloperidol was achieved (section 3.3 at page 208). "Surgically implantable drug delivery" is in the preamble and represents the intended use of the delivery

system while the body of the claim fully defines the claimed composition/product/device. The difference between the claims and Cheng is that the claims recite a range of 20-40% of haloperidol being fabricated into the polymer while Cheng uses 10%. However, it is said on page 209, left column at line 6 that a drug content of from 14.6 to 23.9% can be loaded onto the PLG microspheres. Therefore, taking the teaching of Cheng, one of ordinary skill in the art at the time the invention was made would have reasonable expectation of success to formulate haloperidol loaded biodegradable poly(D,L-lactide-co-glycolide) (PLG) microsphere in which the drug load is 10% or from 14.6 to 23.9%.

Response to Arguments

4. Applicant's arguments filed 06/02/08 have been fully considered but they are not persuasive.

5. a) Applicant argues that the surgically implantable recited in the preamble is not merely a part of the preamble such that the parenterally administrable depot system or injectable depot microsphere of haloperidol fails to anticipate each and every element of the claim and therefore fails to provide prima facie evidence and that there is no reasonable expectation of success in the use of Cheng to deliver 20-40% Haloperidol; implantable devices/system have lasts longer for duration of many months, while injectable systems lasts for days and as such applicant says that the Cheng reference is improperly cited.

aR) The examiner disagrees. The Cheng reference if properly cited. Claim 1 is a device or system or composition that is completely defined by the body of the claim as comprising biodegradable polymer that consists essentially of polylactide or lactide-co-glycolide and 20-40% haloperidol fabricated into an individual surgically implantable implant. In this case the

preamble is the intended use or intended application of a composition and the prior art device/composition/product/device is capable of being surgically implanted. The body of the claim completely and structurally defines the invention such that removal of the intended use preamble from the claim would not affect the structure of the product. Furthermore, introducing the haloperidol by casting and compression molding at a temperature and pressure that allows the haloperidol to flow into the mold is the process of preparing the delivery system containing the polymer and the haloperidol such that the claim read on product by process. Product-by-process claims are not limited to the manipulations of the recited steps, only the structure implied by the steps and "[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985).

It is further noted that the rejection is not one of anticipation as applicant appears to imply but one in which the product is rendered obvious with a difference in the claimed amount of haloperidol and for which it is described in the rejection that left column of page 209 at line 6 contemplates a suggestion that a drug content of from 14.6 to 23.9% can be loaded onto the PLG microspheres.

Regarding implantability and the duration of the device, it is noted that although Cheng talks about injectable system, the system of Cheng is capable of being implanted and the applicant has not disproved that it cannot; the duration of the implant is a function of the

properties of the composition and does not exclude the Cheng system from exhibiting that duration when implanted. "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990).

b) Applicant argues that the maximum theoretical loading of haloperidol in Cheng is 10% while 20-40% is the actual loading in claim 1 and cites left column of page 208 to support the 10% of Cheng and that the 14.6 to 23.9% drug load achieved by Boidron-Celle refers to 5-fluorouracil.

6. bR) The examiner disagrees that Cheng lacks a suggestion that higher drug content cannot be loaded onto the PLG microspheres. While applicant says that the suggested content of 14.6 to 23.9 refers to 5-fluorouracil, the ordinary skilled artisan is capable of implementing this variation even if the variation, and in this case, the loading amount is for 5-fluorouracil as per applicant. Since the implementation is not beyond the skill or the ordinary artisan, the ordinary skilled artisan has the capability of implementing the suggestion for loading of 14.6 to 23.9%, absent a showing that the implementation of the suggestion is beyond the capabilities of the artisan.

c) Applicant argues that there is no suggestion or motivation in Cheng or in the knowledge generally available to one of ordinary skill in the art to modify the teachings of Cheng for a removable drug delivery system. **cR)** The examiner disagrees because applicant has not factually shown that the system of Cheng is not implantable or removable when implanted noting that the polymer of the prior art is the same as the polymer of the claim. Further, Cheng

provides the suggestion for a higher amount of loading of drugs into PLG micropsheres; and the suggestion is a 14.6 to 23.9% loading.

7. Claims 1, 7-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cheng et al., "A poly(D,L-lactide-co-glycolide) microsphere depot system for delivery of haloperidol," in Journal of Controlled Release 55 (1998) 203-212 in view of Domb et al. ("Degradable Polymers for Site-Specific Drug Delivery," in polymers for Advanced Technologies, Vol. 3, pp. 279-292, 1992 for reasons of record and reiterated herein below.

8. Cheng is discussed above as rendering obvious claims 1 and 3. Cheng acknowledges that haloperidol, an antipsychotic drug, is used to treat psychosis such as schizophrenia by oral dosage forms and also as long acting depot injections (section 1). Cheng administers the haloperidol by injecting the composition as a depot. But, implantation/implant reads on depot resulting from depot injections, and it is known to use degradable polymers to deliver drugs to target sites of interest ad described by Domb and carries the advantage that implants are used as site specific drug delivery routes. Therefore, taking the teachings of the references together, one of ordinary skill in the art at the time the invention was made would have reasonable expectation of success to administer the haloperidol antipsychotic drug by implanting it to a site in the schizophrenic subject that would provide sustained release of the antipsychotic agent for a more effective treatment of the condition.

Response to Arguments

9. Applicant's arguments filed 06/02/08 have been fully considered but they are not persuasive.

10. Applicant argues that Cheng does not disclose the 20-40% haloperidol loading, surgical implantation and removability of the implant and that the Domb reference fails to cure this deficiency so that the combined reference does not teach all the claimed elements; that modifying Cheng in view of Domb would be unsatisfactory for its intended purpose;

11. The examiner disagrees. The combined reference teaches the claimed elements. Yes, Cheng does not teach the range, hence the rejection under 35 UISC 103. Yes Cheng suggests higher drug loads into PLGA microspheres, and it flows that the amount of the drug loaded can be optimized. The device of Cheng is capable of being implanted and applicant has not factually shown that it could not be. Cheng suggests higher drug loading onto PLGA microspheres and applicant has not factually shown that higher amounts of drugs, and specifically haloperidol cannot be loaded onto/into the PLGA microspheres as suggested by Cheng. Domb is relied upon for teaching that degradable polymers are known to be used to deliver drugs to target sites with the advantage that implants are used as site specific delivery routes. Therefore, Domb provides reasons for implanting biodegradable drug delivery devices noting that the polymers of claim 1, polylactide or lactide-co-glycolide copolymer are biodegradable, so also are the polymers of the prior art. Contrary to applicant's assertion, implanting the delivery system of Cheng does not make the delivery device to be unsatisfactory for its intended purpose because, Cheng's anticipated goal is to deliver the system as a depot and an implant reads of depot; claim 1 is not an implant formulation but an implantable system that reads on the intended use of the device with the prior art device being capable of being implanted to achieve depot form.

12. Applicant argues that increasing the haloperidol content beyond 15% as disclosed in the examined application would result in crystal formation in Cheng and cites page 208. The examiner disagrees because page 208 does not say that crystal forms at 15% or more haloperidol in the microspheres and would not therefor affect the release profile.

13. Applicant says that Domb is a general review article and that the examiner did not provide the section of Domb that suggests modifying the drug loaded delivery systems that are administered "parenterally intramuscularly" to subcutaneous implant.

14. The examiner disagrees that Domb must teach going from parenteral intramuscular delivery to subcutaneous implantation. However, Domb describes the advantages and disadvantages of these forms of delivery including implantations using biodegradable polymer (see the whole document with emphasis on the abstract, second paragraph, second full paragraph at right column of page 280 and page 281, lines 3-6). The rejection in question is one in which it would be obvious to administer the depot form of Cheng by implantation in order to release haloperidol to a patient for treating pain at the site, the properties or effect of haloperidol being innate to the haloperidol. It is agreed that the Domb reference is a review article, but is a review article that specifically acknowledges and recognizes that in the art biodegradable polymers are utilized as site specific delivery devices (see second paragraph of the abstract on page 279) using implants (second full paragraph of page 280 at the right column). Therefore, the teaching of combined references of Cheng and Domb renders obvious the claimed invention according to the rejections of record.

15. Claims 4 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cheng et al., "A poly(D,L-lactide-co-glycolide) microsphere depot system for delivery of haloperidol," in Journal of Controlled Release 55 (1998) 203-212 in view of Sidman (US 4,450,150) for reasons of record and reiterated herein below.

16. Cheng prepares the haloperidol loaded biodegradable poly(D,L-lactide-co-glycolide) (PLG) microsphere by solvent evaporation (section 2.2). Cheng does not cast the haloperidol dissolved in the solvent in a mold so that Cheng differs from the invention by not molding the haloperidol-polymer solution. However, it is known that implants that deliver drugs to target sites are molded by compressing or injecting the drug formulation as disclosed by Sidman (column 9, lines 8-12; column 10, lines 51-52; column 18, line 29). Therefore, taking the teachings of the references together, one of ordinary skill in the art at the time the invention was made would have reasonable expectation of success to shape the haloperidol antipsychotic drug loaded polymer by injection molding or compression molding to provide a product that would be successfully implanted into the site in the schizophrenic subject that would provide sustained release of the antipsychotic agent for a more effective treatment of the condition.

Response to Arguments

17. Applicant's arguments filed 06/02/08 have been fully considered but they are not persuasive.

Applicant argues that Cheng does not disclose 20-40% haloperidol loading and the examiner agrees that Cheng does not disclose 20-40% haloperidol loading and that is why claim 1 was rejected under 35 USC 103 and by the same token amended claim 1 cannot be rejected under anticipatory rejection as it would apply to the amount of the haloperidol.

Applicant argues that Cheng does not disclose surgical implantation and removability of the implant and that Sidman (US 4,450,150) does not remedy the deficiency and applicant therefore requested the withdrawal of the rejections. The examiner disagrees with applicant as previously noted above that the delivery system of Cheng is capable of being implanted and when implanted the implant is capable of being removed noting that the polymers of the claims and the prior art are the same PLGA.

18. Therefore, the rejections are maintained for reasons of record.

No claim is allowed.

19. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BLESSING M. FUBARA whose telephone number is (571)272-0594. The examiner can normally be reached on 7 a.m. to 5:30 p.m. (Monday to Thursday).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

/Blessing M. Fubara/
Examiner, Art Unit 1618